Office of Environmental Health Hazard Assessment

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Dr. C. W. Jameson
National Toxicology Program, Report on Carcinogens
79 Alexander Drive, Room 3217
P.O. Box 12233
Research Triangle Park, North Carolina 27709

Dear Dr. Jameson:

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) considers the National Toxicology Program (NTP) to be one of the world's leading scientific organizations with respect to the testing and evaluation of chemicals for carcinogenicity. Moreover, the NTP's Report on Carcinogens (RoC) is widely regarded as an authoritative source of information on chemical carcinogens. OEHHA appreciates this opportunity to provide comment on NTP's recently proposed additions and deletions to the Ninth Report on Carcinogens. OEHHA has some concerns related to the implementation of the external peer review process (i.e., the Board of Scientific Counselors RoC Subcommittee) in which chemicals are considered for addition or removal from the RoC. In addition, we are providing comments on diesel exhaust particulates, nickel compounds, ethylene oxide, ethyl acrylate, and methyl tertiary butyl ether (MTBE).

It appears to OEHHA that under the current process the RoC Subcommittee is provided with less than adequate time at their meetings to conduct the in-depth discussions necessary for thorough consideration and deliberation on agents with complex toxicological data sets. It is unclear to us whether the RoC Subcommittee has had adequate opportunity to fully review the original data and other background materials, prior to their meetings. Without such opportunity, they may have been forced to place undue reliance on secondary sources, including reports prepared by subcontractors, and petitions submitted by interested parties. In evaluating the carcinogenicity of agents for which the evidence is complex, the RoC Subcommittee should give primary consideration to original data published in the peer-reviewed scientific literature or submitted according to regulatory guidelines. OEHHA suggests that NTP ensure availability of all necessary original data to the RoC Subcommittee, and where appropriate provide evaluations by NTP's own highly knowledgeable and respected staff, rather than relying on subcontractors or interested parties to provide briefing materials. Also, in order to foster public confidence in the

process, NTP should post the background materials used by the RoC Subcommittee to evaluate each chemical on its Web site.

OEHHA supports the use of mechanistic data in reaching decisions on listings in the RoC, but notes the need for caution and careful evaluation of data in applying this type of information. It is particularly important that mechanistic hypotheses be adequately tested prior to their acceptance and use in hazard identification. All plausible hypotheses, including the null hypothesis, need adequate consideration and exploration of their implications for hazard identification. This may not always be possible, due to the tendency for certain hypotheses to be espoused by energetic protagonists, while other equally valid possibilities receive less than their due consideration. We encourage NTP, as an objective institution, to step in where necessary to develop additional experimental information to test mechanistic hypotheses.

OEHHA supports the decision to list of diesel exhaust particulates as "reasonably anticipated to be a human carcinogen". In 1998, the OEHHA and the Air Resources Board completed a comprehensive risk assessment document on diesel exhaust particulates, entitled "*Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant.*" This enclosed document considers the available scientific evidence as to the health effects of diesel exhaust particulates, and includes a thorough review and analysis of the extensive literature concerning the carcinogenic potential of diesel exhaust. Pursuant to the California regulatory framework, this document was developed via an open, public process with much opportunity for public comment and response as well as independent scientific peer review. The document found that the epidemiological evidence was consistent with a causal relationship between occupational diesel exhaust exposure and lung cancer.

OEHHA supports the decision to upgrade the listing of nickel compounds to "known to be a human carcinogen". Our enclosed document, "Proposed Identification of Nickel as a Toxic Air Contaminant" presents a comprehensive 1991 cancer risk assessment of nickel compounds, including soluble nickel. This document was also developed via an open, public process with much opportunity for public comment and response as well as independent scientific peer review.

OEHHA supports the decision to upgrade the listing of ethylene oxide to "known to be a human carcinogen". We are very much encouraged to see mechanistic and genotoxicity information used by the RoC Subcommittee to support the interpretation of the substantial, but complex, body of evidence for the human and animal carcinogenicity of ethylene oxide.

We would like to comment on the RoC Subcommittee's recommendation to remove the listing of ethyl acrylate as "reasonably anticipated to be a human carcinogen". The decision appears to be based on an untested hypothesis regarding level of risk, rather than hazard

identification. That is, while ethyl acrylate is a reactive molecule with a proven ability to generate genetic damage of the clastogenic type, there is rapid metabolism to inactive products under most conditions *in vivo*. Consequently, the hypothesis is that ethyl acrylate exposure is likely to cause clastogenicity and/or carcinogenesis only at the site of high chemical exposure and humans are not likely to encounter such conditions. It appears that consideration of the likelihood of human exposure to high levels of ethyl acrylate played a significant role in the RoC Subcommittee's decision. In the risk assessment of carcinogens, the hazard identification stage should clearly identify any material capable of causing, or reasonably expected to cause cancer in humans by any route. As shown by NTP (1986), and endorsed by the IARC (1986) evaluation, ethyl acrylate meets this criterion. The likelihood of this outcome under a given set of circumstances with regard to route, level and duration or frequency of exposure is the proper concern of a later stage of the risk assessment process. It is undesirable to confuse these separate stages since this could unjustifiably shield from consideration some other exposure scenario, not presently foreseen, where a significant risk would be predicted by these same considerations and models. Particular caution should be used in the case of ethyl acrylate, where there is an unexplained epidemiological association with colon cancer. Although this latter finding is hard to reconcile with other experimental evidence, it remains possible that future experimental studies or workplace observations will reconcile all these different results. The interpretation of epidemiological studies needs to consider both the power (or lack thereof) of negative findings to exclude certain conclusions, and the confidence which may be placed in any apparent positive associations.

Finally, we wish to comment on the RoC Subcommittee action not to recommend listing MTBE as "reasonably anticipated to be a human carcinogen". We are providing further information on this agent, and wish to request a re-evaluation of MTBE for the 9th or 10th RoC, since the issues raised concerning this agent's carcinogenicity are difficult and need to be looked at in greater depth. At the time of the re-evaluation, new data, including any new analyses, should be considered. This re-review should also consider the toxicological information on the metabolites of MTBE.

The available toxicological data on MTBE have undergone several extensive reviews, analyses, and evaluations this past year in California, as a result of two separate laws enacted by the state legislature during 1997. One comprehensive review was conducted by the University of California; several other reviews were conducted by OEHHA. In each report that evaluated the evidence of carcinogenicity of MTBE, a conclusion was reached that MTBE is an animal carcinogen with the potential to cause cancer in humans. The purpose, scope, and conclusion of each of these recent California health-based evaluations of MTBE are briefly discussed below.

The MTBE Public Health and Environmental Protection Act of 1997 directed the University of California to conduct an assessment of the health and environmental effects of

MTBE. Volume II of this November 1998 *Health and Environmental Assessment of MTBE. Report to the Governor and Legislature of the State of California as Sponsored by SB 521*, contains an exhaustive evaluation of the health effects of MTBE. This evaluation includes a thoughtful and extremely thorough evaluation of the evidence relevant to carcinogenicity and carefully examines the various criticisms and issues raised regarding the completeness and appropriateness of the reporting and analysis of the bioassay data, and the relevance of the observed tumor sites to human cancer risk. The report states "Based on a thorough review of these carcinogenicity studies, supporting data on pathology and mechanisms of tumor induction, and carcinogenicity studies of MTBE's primary metabolites (TBA and formaldehyde), we conclude that MTBE is an animal carcinogen with the potential to cause cancer in humans". We are enclosing Volume II: *An Evaluation of the Scientific Peer-Reviewed Research and Literature on the Human Health Effects of MTBE, its Metabolites, Combustion Products and Substitute Compounds*, for your consideration.

The Local Drinking Water Protection Act of 1997 directed the California Department of Health Services to develop a primary maximum contaminant level (MCL) that addresses health concerns, by July 1, 1999. In accordance with California procedures for development of such primary MCLs, DHS requested OEHHA to conduct a risk assessment on MTBE. In the meantime, the California Safe Drinking Water Act of 1996 requires OEHHA to adopt Public Health Goals (PHGs) for contaminants in drinking water based exclusively on public health considerations. Therefore, OEHHA developed a document entitled "*Public Health Goal for MTBE in drinking water*", which included the derivation of a numeric PHG for levels of MTBE in drinking water based on carcinogenic effects observed in experimental animals. In evaluating the evidence relevant to carcinogenicity, this assessment addressed the appropriateness of the reporting and analysis of the bioassay data and the relevance of the observed tumor sites to human cancer risk. The document states: "As a result of this assessment OEHHA considers MTBE to be an animal carcinogen and a possible human carcinogen". We are submitting the June 1998 draft of this document, *Public Health Goal for Methyl Tertiary Butyl Ether (MTBE) in Drinking Water*, for your consideration. The final draft should be completed by the end of this month.

The Local Drinking Water Protection Act of 1997 also required the State's qualified experts (i.e., the Carcinogen Identification Committee and the Developmental and Reproductive Toxicants Identification Committee) for the Safe Drinking Water and Toxic Enforcement Act of 1986, also known as Proposition 65, to make a finding on or before January 1, 1999 as to whether MTBE has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity. In support of this requirement, OEHHA developed documents evaluating the evidence on the carcinogenicity and the reproductive toxicity of MTBE. The document addressing the evidence relevant to carcinogenicity of MTBE contains an extensive discussion of the issues raised regarding the

appropriateness of the reporting and analysis of the bioassay data, and the relevance of the observed tumor sites to human cancer risk. We are submitting the October 1998 draft of this document, *Evidence on the Carcinogenicity of Methyl Tertiary Butyl Ether (MTBE)*, for your consideration. The Carcinogen Identification Committee met on December 10, 1998 and considered MTBE. Although a formal vote on MTBE was not taken by the Committee, a polling of the six members in attendance indicated that the four affirmative votes necessary for listing MTBE as causing cancer would not be forthcoming (three Committee members indicated that they would vote in favor of listing, three indicated they would not, and one member was not present).

If you would like additional information about OEHHA's activities related to carcinogen hazard identification or have specific questions about the enclosed OEHHA documents, please call Dr. Martha Sandy, Chief of the Cancer Toxicology Unit at (510) 622-3192.

Sincerely

George V. Alexeeff, Ph.D., DABT
Deputy Director for Scientific Affairs

Enclosures

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